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DOI:

[10.1016/j.paid.2014.10.024](https://doi.org/10.1016/j.paid.2014.10.024)

Document Version

Peer reviewed version

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Citation for published version (APA):

Ruffle, J. K., Farmer, A. D., Kano, M., Giampietro, V., Aziz, Q., & Coen, S. J. (2015). The influence of extraversion on brain activity at baseline and during the experience and expectation of visceral pain. *Personality and Individual Differences*, 74, 248-253. [10.1016/j.paid.2014.10.024](https://doi.org/10.1016/j.paid.2014.10.024)

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Manuscript Number: PAID-D-14-00446R1

Title: The influence of extraversion on brain activity at baseline and during the experience and expectation of visceral pain

Article Type: Research Paper (<5000 words)

Section/Category: Regular Issue

Keywords: Extraversion; Visceral Pain; fMRI; Human Brain; Pain Anticipation; Personality.

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Abstract: Eysenck proposed a 'trait theory' of personality, the dimensions of which encompass numerous individual qualities. Whilst the influence of neuroticism on the brain processing of pain is well described, the role of extraversion, to date, has not been systematically investigated. Our aim was to address this knowledge gap using functional magnetic resonance imaging (fMRI). Extraversion was measured in 33 healthy volunteers (17 male, mean age 29 years [range 20-53]) using the Eysenck Personality Questionnaire. fMRI data were acquired using a 3T MRI scanner during rest, pain anticipation, and painful oesophageal balloon distention. The effect of extraversion on fMRI responses was determined. Extraversion scores varied (range 6-22) and did not influence pain threshold or rating. High extraversion was associated with significantly greater activity in the left cuneus during rest ($p \leq 0.001$), and the right insula during both anticipation ($p \leq 0.0002$) and pain ($p \leq 0.0008$). Low extraversion was associated with significantly greater brain activity in the bilateral precuneus, bilateral lingual gyrus, right inferior temporal gyrus, left fusiform gyrus and left superior parietal lobule during pain anticipation (all $p \leq 0.0001$). These results suggest that extraversion is associated with differences in the brain processing of visceral pain. Future studies of visceral pain, using fMRI, should control for extraversion.



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26th September 2014

Subject: Submission of revised manuscript entitled "The influence of extraversion on brain activity at baseline and during the experience and expectation of visceral pain."

Dear Professor Vernon,

Please find enclosed our revised manuscript entitled "The influence of extraversion on brain activity at baseline and during the experience and expectation of visceral pain", by Ruffle et al., for further consideration for publication in your journal *Personality and Individual Differences*.

Following the kind suggestions of both the editor and reviewer, the article has been significantly improved. We hope you find these changes sufficient, and that they respond to the comments accordingly.

We feel this manuscript makes an important contribution to knowledge of the influence of inter-individual factors, such as the personality trait extraversion, on the subjective perception and brain processing of visceral pain. We anticipate this will be of interest to the journal readership and will provide researchers with important information for future research studies involving brain imaging of personality and pain processing.

Total word count: 4995.
Conflicts of interest: None declared.

Role of the funding source:

This research was funded by a British Academy Grant held by Dr Steven Coen. Dr Adam Farmer was funded by a Medical Research Council project grant - MGAB1A1R. Professor Qasim Aziz was also funded by the Medical Research Council. Qasim Aziz and Steve Coen acted as joint senior authors on this manuscript. The funding sources had no involvement in the study other than financial support.

We look forward to hearing from you in due course.

Yours Sincerely,

A handwritten signature in black ink, appearing to be "JR", followed by a long, sweeping horizontal line.

James Ruffle, BSc.

REVIEWER COMMENTS TO THE AUTHORS

Editor Comment: Please ensure that your revised paper meets PAID formatting requirements.

Response: The revised paper has been prepared in accordance with the PAID formatting guidelines.

We would like to thank the reviewer for their helpful comments in allowing us to improve our manuscript. We have addressed the comments of the reviewer which we think have greatly improved the manuscript. Herein, we provide a detailed point by point response to the comments made.

Comment 1: The introduction provides some useful information about the literature contributing to the current paper; however, it is not synthesized in a way that leads the reader to fully understand why the current paper is necessary. There is some mention in the discussion of the utility of understanding the relationship between extraversion and brain functioning (comparing to neuroticism, utility in clinical settings); adding a justification to the introduction for the study would add significant utility to the paper. As it is now, I don't quite understand why the study was completed beyond a simple exploratory investigation. A hypothesis is necessary and will guide the reader through the paper. This does not need to be a specific prediction of the brain systems that will show activation, but a reason for exploring the relationship is necessary.

Response: We agree with the reviewer that the introduction was lacking a clear rationale and did not emphasize the fact the study builds on recent findings conducted on visceral pain processing and personality. The introduction has now been rewritten in light of the reviewer's useful suggestions. The introduction now commences with a definition of visceral pain (thus incorporating comment 6), followed by an overall introduction to the concept of psychophysiological factors influencing brain pain processing. A description of extraversion is retained as per the original submission, but there is further detail added regarding the interplay of personality and pain processing. Lastly, we have taken onboard the helpful comments of the reviewer and described a clearer justification for the study throughout the introduction.

Comment 2: In the conclusion, remove statements implying causality or influence of extraversion on brain functioning. The paper is a cross-sectional paper, so causality cannot be supported. Examples of language implying causality include "extraversion influence brain processing," and "extraversion affects neural low frequency oscillations." It would also strengthen the paper to clarify statements such as "our data have confirmed the importance of extraversion under experimental conditions of pain" by describing the importance, or to avoid the statements altogether.

Response: We appreciate the reviewer's comments and agree that we somewhat over emphasized the findings of our study such that it appeared we were suggesting a causal relationship. As suggested by the reviewer, all statements implying causality have now been removed from both the discussion and conclusion. Unclear statements have been either rewritten or removed.

Comment 3: The paper is diluted somewhat by the use of language that is unnecessarily flowery, sometimes to the point of being of questionable accuracy (e.g. "Whilst one's physicality, anatomical composition, and physiological bodily systems are common to all, the inherent constitution of the psyche is personality, which arguable contributes to an individual's weakness."). Editing the prose for the sake of parsimony will considerably strengthen the paper.

Response: The introduction and discussion of the manuscript has been rewritten in light of the reviewer's useful suggestions.

Comment 4: Though the authors explained their dichotomization rationale for extraversion, I still feel that their method of dichotomizing may have artificially depressed their results and muddled the concept of low vs high personality traits. By dichotomizing participants at the median, the authors have treated extraversion as though there is no average range, which is inaccurate. Perhaps splitting groups at ± 1 standard deviation from the mean would better suit the author's goals.

Response: Whilst splitting the groups at ± 1 SD, similar to that by (Leon, 1974), is a reasonable methodology, it would eliminate the majority of the cohort and significantly lower study power. As the study was one of healthy volunteers, there are a large number of volunteers who score within 1SD of the mean. The mean of 17.06 \pm 4.22 (SD) would reduce the low and high extraversion cohorts to an N of 5 and 4 respectively – far too low for a neuroimaging study, where individual variability can be highly influential. Large cohorts are required to maintain study power. This cohort of 33 is one of the largest that has been published in fMRI with visceral pain (see (Mayer, et al., 2009), and is a strength to the prospective paper.

Consequently, we believe there is justification to retain the median split analysis. Other groups have also previously used median split analysis, yielding interesting results (Drabant, et al., 2011; Walter, et al., 2011). This includes a similar study where the relationship between neuroticism and somatic pain were investigated (Drabant, et al., 2011).

Lastly, it is recognized that the reviewer's suggested analysis of ± 1 SD from the mean is a useful one. Despite the aforementioned problems of analyzing using the mean ± 1 SD for analysis in this particular study, we have now included in the manuscript 'Limitations' a requirement for further studies using the methodology suggested.

Comment 5: The point being made in the discussion is difficult to identify. I feel that a strong discussion could focus on the findings that there are different brain structures associated with low and high extraversion, the clinical and empirical utility of the findings, and the way in which the current study leads to future research. Certain components of the discussion are distracting and may not warrant inclusion (e.g. comparing findings to neuroticism while suggesting that comparison is not indicated because of differing methodology). A reorganization of the discussion centered around the strong findings and leading from the current exploratory work to future theoretical paper would be a strong ending to the paper.

Response: The discussion has been rewritten. As kindly suggested by the reviewer, the

discussion now focuses on the findings that high and low extraversion are associated with disparate brain activity during the experimental conditions, including rest. As highlighted by the reviewer, parts of the discussion that were distracting have been removed. With regards to the utility of the findings – the conclusion discusses how evaluating personality traits has been suggested by (Ramirez-Maestre & Esteve, 2013) to be efficacious in guiding pain intervention therapies and even treatment outcomes.

Comment 6: Define "visceral" pain

Response: The introduction has now been rewritten in light of the reviewer's comments. The introduction now commences with a definition of pain, as per (IASP, 1994). This is followed by a definition of visceral pain.

Comment 7: Sentence structure is clumsy in some areas, mainly the introduction and discussion section

Response: The introduction and discussion has been rewritten in light of the reviewer comments.

Comment 8: Report p levels at 2 decimal points

Response: This has now been corrected.

Comment 9: The figure describing the study design is difficult to understand, edit for parsimony or remove.

Response: As kindly suggested, the figure has been altered and simplified to describe the time course for a single trial. Similarly the figure legend has been edited for parsimony.

REFERENCES

- Drabant, E. M., Kuo, J. R., Ramel, W., Blechert, J., Edge, M. D., Cooper, J. R., Goldin, P. R., Hariri, A. R., & Gross, J. J. (2011). Experiential, autonomic, and neural responses during threat anticipation vary as a function of threat intensity and neuroticism. *Neuroimage*, 55, 401-410.
- IASP. (1994). *Part III: Pain Terms, A Current List with Definitions and Notes on Usage* (Second Edition ed.). Seattle: IASP Press.
- Leon, B. N. (1974). Pain perception and extraversion. *Percept Mot Skills*, 38, 510.

Mayer, E. A., Aziz, Q., Coen, S., Kern, M., Labus, J. S., Lane, R., Kuo, B., Naliboff, B., & Tracey, I. (2009).

Brain imaging approaches to the study of functional GI disorders: a Rome working team report.

Neurogastroenterol Motil, 21, 579-596.

Ramirez-Maestre, C., & Esteve, R. (2013). Disposition and adjustment to chronic pain. *Curr Pain*

Headache Rep, 17, 312.

Walter, S., Kessler, H., Gruss, S., Jerg-Bretzke, L., Scheck, A., Strobel, J., Hoffmann, H., & Traue, H. C.

(2011). The influence of neuroticism and psychological symptoms on the assessment of images in

three-dimensional emotion space. *Psychosoc Med*, 8, Doc04.

TITLE

The influence of extraversion on brain activity at baseline and during the experience and expectation of visceral pain

AUTHORS

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HIGHLIGHTS

- Herein we investigate the role of extraversion in brain processing of visceral pain
- High extraversion corresponded to greater baseline activity in the left cuneus
- High extraversion conferred greater right insula activity in anticipation and pain
- Low extraversion conferred greater occipital region activity during anticipation
- Future brain imaging studies of visceral pain should control for extraversion

ABSTRACT

Eysenck proposed a ‘trait theory’ of personality, the dimensions of which encompass numerous individual qualities. Whilst the influence of neuroticism on the brain processing of pain is well described, the role of extraversion, to date, has not been systematically investigated. Our aim was to address this knowledge gap using functional magnetic resonance imaging (fMRI).

Extraversion was measured in 33 healthy volunteers (17 male, mean age 29 years [range 20-53]) using the Eysenck Personality Questionnaire. fMRI data were acquired using a 3T MRI scanner during rest, pain anticipation, and painful oesophageal balloon distention. The effect of extraversion on fMRI responses was determined.

Extraversion scores varied (range 6-22) and did not influence pain threshold or rating. High extraversion was associated with significantly greater activity in the left cuneus during rest ($p \leq 0.001$), and the right insula during both anticipation ($p \leq 0.0002$) and pain ($p \leq 0.0008$). Low extraversion was associated with significantly greater brain activity in the bilateral precuneus, bilateral lingual gyrus, right inferior temporal gyrus, left fusiform gyrus and left superior parietal lobule during pain anticipation (all $p \leq 0.0001$).

These results suggest that extraversion is associated with differences in the brain processing of visceral pain. Future studies of visceral pain, using fMRI, should control for extraversion.

KEYWORDS

Extraversion; Visceral Pain; fMRI; Human Brain; Pain Anticipation; Personality

1. Introduction

Pain is defined by the International Association for the Study of Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage(IASP, 1994). Visceral pain refers to this sensation from any of the large interior organs from bodily cavities, for example the gastrointestinal tract, and is a central defining feature of common gastrointestinal disorders such as irritable bowel syndrome.

The experience of visceral pain is influenced by numerous inter-individual differences including genetic, physiological, neuroanatomical, and psychophysiological factors(Farmer, et al., 2013). Of the psychophysiological factors, personality is thought to be highly influential in pain interpretation(Eysenck, 1947, 1973). However, much of our understanding of the effect of personality on pain processing is derived from somatic pain research, leaving the role of personality in visceral pain processing poorly understood.

Early studies using somatic pain suggest extraversion influences pain threshold(Barnes, 1975; Eysenck, 1947, 1973), supporting Eysenck's theory of personality that proposed extraverts have diminished pain sensitivity reflected in higher thresholds and tolerance to pain than introverts(Eysenck, 1947, 1973).

Contemporary findings support these early observations, which demonstrate that specific phenotypes of sensation-seeking (a dimension of extraversion) have lowered

Abbreviations: L_E, low extraversion; H_E, high extraversion

sensitivity to cold pressor pain(Lee, Watson, & Frey Law, 2010; Vassend, Roysamb, & Nielsen, 2013). Other recent work has shown that high extraversion scoring healthy volunteers tolerate greater duration of experimental pain than those scoring low in extraversion(Ferracuti & De Carolis, 2005). Finally, higher extraversion has been linked to active pain coping strategies and lower reported intensity of pain(Ramirez-Maestre, Lopez Martinez, & Zarazaga, 2004).

Recent evidence has demonstrated the importance of personality in inter-individual differences in the experience of visceral pain. In a sample of healthy volunteers, Farmer et al. have shown high neuroticism forms part of a pain sensitive phenotype whose characteristics including reduced pain tolerance to painful visceral distention (Farmer, et al., 2013). In contrast, higher extraversion was associated with increased pain tolerance. Interestingly, in a follow-up study the pain sensitive phenotype was shown to be over-represented in functional chest pain patients; a clinical population characterized by chronic visceral pain(Farmer, et al., 2014). Given that personality is a central factor of these phenotypes, it is plausible to suggest that some of the mechanisms in determining these differences may have a neurological basis. Indeed, we have built on the study above by describing brain regions involved in the relationship between neuroticism level and visceral pain processing(Coen, et al., 2011). However, the interaction between extraversion and the brain processing of visceral pain has yet to be reported. Our aim was to address this knowledge-gap by using fMRI to investigate the role of extraversion on brain activity at rest, during pain anticipation and processing of visceral pain.

2. Materials & Methods

2.1 Subjects

Thirty-three healthy volunteers (17 male; mean age 29 years, range 20-53; all right handed) participated in the study, all of whom provided informed written consent. The study was approved by the local ethics committee (reference CREC/07/08-7). Participants were screened for a previous history of psychiatric or gastrointestinal symptoms, and were not receiving any medications. All volunteers were assessed for degree of extraversion (range 0-23, where a higher score represents higher extraversion) using the Eysenck Personality Questionnaire-Revised (EPQ-R)(Eysenck & Eysenck, 1991). Participants additionally completed the Spielberger State and Trait Anxiety (STAI) Questionnaire (range 20-80, where a higher score equates to higher anxiety) assessing degree of anxiety on the day of scanning (state) and general anxiety (trait)(Spielberger, Gorsuch, & Lushene, 1970).

All 33 volunteers were dichotomized by means of a median split based on an extraversion score of 18, a method previously utilized in multiple personality studies (including neuroimaging)(Drabant, et al., 2011; Walter, et al., 2011). Consequently a score of 17 or below was allocated to the low extraversion (L_E) group, whilst a score of 18 and above was allocated to the high extraversion (H_E) group. The L_E group consisted of 14 subjects (score range 7-17), whilst the H_E group consisted of the remaining 19 subjects (score range 18-22).

2.2 Visceral Pain Induction – Oesophageal Stimulation

Immediately prior to the experiment, a 3-mm catheter (Sandhill Scientific, Oxford, UK), with a 2-cm balloon mounted on its distal tip was positioned in the distal oesophagus with the mid point of the balloon positioned 35cm *ab nares*. A one second mechanical painful stimulus to the oesophagus was subsequently delivered via balloon distention, as previously described by (Coen, et al., 2009). Sensory threshold (ST) and pain tolerance threshold (PTT) were determined in each subject by recurrent automated 2-ml increments of balloon dilation until the point of first sensation (ST), and when the stimuli could no longer be tolerated (PTT). Subsequently, subjects were positioned in the MRI scanner, and the pre-elicited PTTs were used for the painful stimuli during the experiment.

2.3 Functional Magnetic Resonance Imaging Experimental Procedure

An event-related design with 3 conditions was employed. These were as follows: 1) the anticipation of pain, 2) the delivery of the painful visceral stimulus and 3) a 'safe' period, during which subjects were informed they would not receive any painful distensions. Subjects were able to rate the intensity of each painful stimulus by using an electronic visual analogue scale (VAS). To measure a subject's anticipation, a visual cue program was used (developed in conjunction with the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London). The experiment consisted of 20 trials, with 60 events in total examined - 20 each for anticipation, pain and null events (rest/baseline)(Figure 1). Each trial commenced with a visual warning cue projected on the screen for between 3-12 seconds, as a coloured square, denoting that a painful stimulus was imminent, thus serving as a

model for anticipation. Subsequently a 1-second painful oesophageal stimulus was delivered (at the subject's pre-elicited PTT), that was followed by a second differently coloured square, being projected for 28-35 seconds, signaling safety from the stimulus. The safety interval was additionally used to model the baseline or rest condition to which other conditions were compared. The length of anticipatory and safety periods were pseudo-randomised and jittered to the TR (repetition time). The start of the anticipatory phase represented the commencement of the next trial. Variability in event duration was employed to limit habituation and maximize effectiveness of the anticipatory cue (Carlsson, et al., 2006). The colour cues attributed to either rest or anticipation were pseudo-randomised to prevent any colour bias. Half of the subjects received a blue square for anticipation and a yellow square for safety, whilst the other subjects received the opposite.

2.4 Pain Ratings

During the safety period, the VAS was used to measure each individual's subjective evaluation of the degree of pain elicited by the stimulus. This was performed using an MRI compatible button box (held in the right hand). The VAS scale was randomised to appear on the screen 9-15 seconds after the painful event, and was presented for 5 seconds. Scored out of 100, 0 indicated no sensation (sub-ST), 50 indicated a moderate level of discomfort, whilst 100 signified the worst pain imaginable.

2.5 Functional Magnetic Resonance Data Acquisition

FMRI data were obtained using a General Electric Signa Excite HDxt II 3.0 Tesla scanner, located at the Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London. Head movement was minimized by the application of foam padding within the head coil. During scanning, subjects could view a screen that projected the aforementioned coloured squares and VAS. In preparation for fMRI, high-resolution gradient echo structural scans (43x3mm slices, 0.3 interslice gap, echo time (TE) 30ms, TR 3000ms, flip angle 90°, matrix size 128², in-plane voxel size 1.875x1.875) were acquired for Talairach data normalisation. The fMRI data consisted of 480 T2* weighted images per slice (40x3mm slices, 0.3 interslice gap, TE 30ms, TR 2500ms, flip angle 80°, matrix size 64², in-plane voxel size 3.75x3.75, sum of images per scan = 19,200) that demonstrated blood oxygen level dependent (BOLD) contrast during the different experimental events.

2.6 Data Analysis

2.6.1 Statistical Analysis of Psycho-behavioural Data

Results are presented as mean (\pm standard error of the mean (SEM)), medians and ranges dependent on data type, determined by Shapiro-Wilk testing. For quantitative psychophysiological data, differences between the groups were assessed using unpaired t-tests or Mann Whitney U-tests depending on data distribution. Correlational analyses were performed using Pearson's correlation. Two-tailed tests were used throughout. $P < 0.05$ was adopted as the statistical criterion for significance. All analyses were performed using proprietary software

(GraphPad Prism version 6.00, GraphPad Software, La Jolla California, USA, www.graphpad.com).

2.6.2 Analysis of fMRI Data by Brain Activation Mapping

All experimental fMRI data were analysed with XBAM version 4.1 (<http://brainmap.co.uk/>), a statistical package of image processing and statistical inference created at the Institute of Psychiatry, King's College London. XBAM uses non-parametric statistics in order to minimise assumptions on the nature of the data (Brammer, et al., 1997; Bullmore, et al., 1996). Median statistics are used to control for outliers, and the package standardises for inter-individual variability of residual noise by the use of permutation testing. Before brain activation mapping procedures, all fMRI data were pre-processed and individual brain maps were obtained.

2.6.3 Analysis of Variance for Brain Activation Mapping

An ANOVA was used with XBAM to compare the responses between groups (in this case L_E versus H_E) by fitting data at every voxel using the linear model $Y = a + bX + e$. 'Y' denotes the magnitude of the BOLD response per subject, whilst 'X' denotes a contrast matrix for each group (such as high extraversion). In addition, 'a' denotes the mean effect for all subjects of a group, 'b' is the difference between groups and 'e' is the vector of error. Following the above, the sum of absolute deviations is minimised to fit the model in order to reduce outlier effects (in opposition to the sum of squares (as per a normal statistical ANOVA)). By permutation of data between groups or conditions, the null distribution of b is calculated (assuming a null

hypothesis of no difference between the groups/conditions). Within the analysis, statistical thresholds were allocated to yield ≤ 0.5 false positive 3D cluster per brain.

3. Results

3.1 Psychometric Data

The mean \pm SEM extraversion score for all 33 subjects was 17.06 ± 0.73 (Figure 2). There were no significant differences between male ($n=17$) and female ($n=16$) participants' extraversion scores (16.88 ± 1.20 vs. 17.25 ± 0.86 respectively, $p=0.81$). No correlations were demonstrable between extraversion scores and all other demographics or physiological variables (age $p=0.25$, PTT $p=0.23$, ST $p=0.23$ and VAS $p=0.63$).

3.2 Physiological Characteristics

All 33 subjects tolerated the procedure well. Mean VAS ratings for the painful stimuli during scanning were within the painful range (mean VAS 64.21 ± 1.99 (range 36-90)). The mean balloon inflation (ml) to reach sensory and pain thresholds was 7.33 ± 0.96 and 22.61 ± 1.27 respectively. STs and PTTs were significantly different ($p \leq 0.0001$).

3.3 Effect of Extraversion

3.3.1 Low vs. High Extraversion Subgroups

Extraversion scores between the two groups significantly differed (L_E mean 13 ± 0.86 and H_E mean 20.05 ± 0.32 , $p \leq 0.0001$) (Figure 3 and Table 1). The L_E group consisted of 6 males and 8 females, mean age 32 years (range 22-53), whilst the higher

extraversion H_E group consisted of 11 males and 8 females, mean age 28 years (range 20-48). The ages and gender distribution between the two groups did not differ significantly.

3.3.2 Psychometrics and Behavioral Data

Mean \pm SEM state anxiety scores for both L_E and H_E were 30.93 ± 2.10 and 29.16 ± 1.54 , and did not significantly differ ($p=0.49$). Mean \pm SEM trait anxiety scores for L_E and H_E were 33.64 ± 1.80 and 34.53 ± 2.64 , which also did not significantly differ ($p=0.80$). The mean VAS scores for L_E and H_E were 61.79 ± 3.99 and 66.00 ± 1.81 , respectively. The mean \pm SEM ST for the L_E and H_E groups were 8.29 ± 2.01 and 6.63 ± 0.79 , respectively. The mean PTT for both L_E and H_E cohorts were 21.86 ± 2.36 and 23.16 ± 1.40 , respectively. There was no significant difference between VAS ($p=0.30$), ST ($p=0.35$) and PTT ($p=0.64$) across the two groups.

3.4 Brain Activity During Rest, Pain Anticipation and Visceral Pain

3.4.1 Baseline Brain Activity

During the modeled rest period, subjects of the H_E group displayed significantly greater activity in the left cuneus (Brodmann area [BA] 18), compared to brain activity of the L_E group ($p \leq 0.001$) (Table 2 and Figure 4).

3.4.2 Brain Activity During Pain Anticipation

During anticipation of the painful visceral stimulus, subjects of the L_E group displayed (in descending order of 3D cluster size, in voxels) significantly greater activity in the bilateral precuneus (BA31 & BA7) ($p \leq 0.0001$), bilateral lingual gyrus

(BA18)($p \leq 0.0001$), bilateral cerebellum ($p \leq 0.0001$), right inferior temporal gyrus ($p \leq 0.0001$), left fusiform gyrus (BA37)($p \leq 0.0002$), left superior parietal lobule (BA7)($p \leq 0.0001$), left inferior occipital gyrus (BA18)($p \leq 0.0002$), and right paracentral lobule (BA6)($p \leq 0.0001$) when compared to brain activity in the H_E group (Table 3 and Figure 5). Subjects of the H_E group displayed significantly greater activity in the right insula during this same anticipatory period ($p \leq 0.0002$) (Table 2 and Figure 4).

3.4.3 Brain Activity During Visceral Pain

During the actual painful stimulus, subjects of the H_E group showed significantly greater activity in the right insula, compared to activity in the L_E group ($p \leq 0.0008$) (Table 2 and Figure 4).

4. Discussion

We have demonstrated that the brain processing of experimental oesophageal pain in healthy subjects differs, depending on high or low extraversion score. To our knowledge, this is the first time these findings have been demonstrated.

4.1 Behavioural Data

Although previous research has suggested that somatic PTT is influenced by extraversion (Barnes, 1975; Eysenck, 1947, 1973), we found no objective evidence to support this assertion for visceral pain, despite differences in brain activity. This could be due to differences in visceral and somatic pain processing or perhaps our limited sample size of healthy volunteers. Indeed, although differences between groups did not meet the statistical threshold, there was a trend for the high

extraversion group to tolerate higher balloon volumes compared to the low extraversion group. Thus, it is plausible to suggest that these data may have reached significance if the sample size was larger, such as in the study described by (Farmer, et al., 2013)(n=120), which did show increased tolerance to balloon distension in more extravert subjects. Consistent with previous evidence, we observed that extraversion did not affect an individual's subjective rating of visceral pain(Farmer, et al., 2013).

4.2 Extraversion and Brain Activity During Anticipation of Pain

In high extraversion subjects, we report significantly greater brain activity in the right insula during pain anticipation. The threat of pain is an emotional experience which precipitates a state of heightened arousal, and therefore activity in the insula is perhaps expected given its complex role in encoding both the sensory and affective dimensions of pain(Van Oudenhove, Coen, & Aziz, 2007). Moreover, the insula has been shown in previous studies to have a role in brain processing of visceral pain anticipation(Coen, et al., 2011; Yaguez, et al., 2005). The fact that activity is higher in the high extraversion group is interesting and may support the theory that higher extraversion individuals show greater change in brain activity (from a low baseline cortical arousal) in brain regions involved in cognitive and emotional processing when confronted with an emotionally and cognitively salient stimulus(Kehoe, Toomey, Balsters, & Bokde, 2012; Kumari, ffytche, Williams, & Gray, 2004).

4.3 Extraversion and Brain Activity During Pain

During pain, high extraversion was associated with greater activity in the right insula. As described above, the right insula is associated with visceral pain perception, the processing of its affective dimension and modulation by attention and reappraisal (Aziz, et al., 1997; Van Oudenhove, et al., 2007). Interestingly, insula activity during pain has previously been correlated with the autonomic (namely sympathetic) response to heat pain (Seifert, et al., 2013). Furthermore, extraversion has been shown to relate to a predominantly sympathetic response during visceral pain, when compared to neuroticism (Farmer, et al., 2013). Taken together, these findings suggest insula activity in the current study may represent a greater sympathetic response during pain in the high extraversion group.

4.4 Extraversion and Resting Period Brain Activity

During rest, high extraversion subjects showed significantly greater activity in the left cuneus. Whilst this occipital region is implicated visual processing, it is also associated with risk-taking (Tamura, et al., 2012). A well-discussed sub-dimension of extraversion is sensation-seeking/risk taking behaviors (Vassend, et al., 2013). Contemporaneous data has demonstrated that problematic gamblers had significantly greater activity as compared to controls in the cuneus when shown a video of individuals undertaking gambling activities (Crockford, Goodyear, Edwards, Quickfall, & el-Guebaly, 2005). Therefore, it is possible that the observed cuneus activity is a reflection of a risk-taking dimension of extraversion. This finding is consistent with previous evidence that perfusion in the cuneus is associated with

novelty seeking(O'Gorman, et al., 2006). However, further studies are required as we evaluated extraversion in general, as opposed to risk taking.

4.5 Limitations

We used a median split in order to dichotomize our study sample into groups of high and low extraversion. This approach was driven by the study cohort and it could be argued this split was somewhat arbitrary and potentially biased by our sample. However, the results show a good range of extraversion scores within the study sample and demonstrate that, following the split, the two groups differed significantly on extraversion levels such that they fell into categories of high and low scores. Furthermore, this approach to categorising groups based on personality trait scores builds on previous studies (including neuroimaging) that have adopted the same method(Drabant, et al., 2011; Walter, et al., 2011). Future studies however could build on our current findings by investigating extraversion and brain activity using subjects scoring at extreme ends of the extraversion spectrum.

5. Conclusions

These data illustrate a novel role for degree of extraversion and brain activity during rest, anticipation of pain and pain perception. A recent study concluded that evaluation of personality traits in a clinical setting is likely beneficial in guiding pain intervention therapies(Ramirez-Maestre & Esteve, 2013). These findings, implicating extraversion to influence pain processing at the neural level, confirm the notion of evaluating personality in a clinical setting to be advantageous. The study shows disparity in brain activity between the introvert and extravert brain. This likely

reflects the identification of a variable partly accountable for inter-individual variability in brain activity during visceral pain. These data may reflect a necessity to evaluate personality in pain research to maintain control of experimental variables.

REFERENCES

- Aziz, Q., Andersson, J. L., Valind, S., Sundin, A., Hamdy, S., Jones, A. K., Foster, E. R., Langstrom, B., & Thompson, D. G. (1997). Identification of human brain loci processing esophageal sensation using positron emission tomography. *Gastroenterology*, *113*, 50-59.
- Barnes, G. E. (1975). Extraversion and pain. *Br J Soc Clin Psychol*, *14*, 303-308.
- Brammer, M. J., Bullmore, E. T., Simmons, A., Williams, S. C., Grasby, P. M., Howard, R. J., Woodruff, P. W., & Rabe-Hesketh, S. (1997). Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. *Magn Reson Imaging*, *15*, 763-770.
- Bullmore, E., Brammer, M., Williams, S. C., Rabe-Hesketh, S., Janot, N., David, A., Mellers, J., Howard, R., & Sham, P. (1996). Statistical methods of estimation and inference for functional MR image analysis. *Magn Reson Med*, *35*, 261-277.
- Carlsson, K., Andersson, J., Petrovic, P., Petersson, K. M., Ohman, A., & Ingvar, M. (2006). Predictability modulates the affective and sensory-discriminative neural processing of pain. *Neuroimage*, *32*, 1804-1814.
- Coen, S. J., Kano, M., Farmer, A. D., Kumari, V., Giampietro, V., Brammer, M., Williams, S. C., & Aziz, Q. (2011). Neuroticism influences brain activity during the experience of visceral pain. *Gastroenterology*, *141*, 909-917 e901.
- Coen, S. J., Yaguez, L., Aziz, Q., Mitterschiffthaler, M. T., Brammer, M., Williams, S. C., & Gregory, L. J. (2009). Negative mood affects brain processing of visceral sensation. *Gastroenterology*, *137*, 253-261, 261 e251-252.
- Crockford, D. N., Goodyear, B., Edwards, J., Quickfall, J., & el-Guebaly, N. (2005). Cue-induced brain activity in pathological gamblers. *Biol Psychiatry*, *58*, 787-795.
- Drabant, E. M., Kuo, J. R., Ramel, W., Blechert, J., Edge, M. D., Cooper, J. R., Goldin, P. R., Hariri, A. R., & Gross, J. J. (2011). Experiential, autonomic, and neural responses during threat anticipation vary as a function of threat intensity and neuroticism. *Neuroimage*, *55*, 401-410.
- Eysenck, H. J. (1947). *Dimensions of Personality*. London: Kegan Paul.
- Eysenck, H. J. (1973). *Eysenck on Extraversion*: John Wiley & Sons.

- Eysenck, H. J., & Eysenck, S. B. G. (1991). *Manual of the Eysenck Personality Scales*. London, UK: Hodder and Stoughton.
- Farmer, A. D., Coen, S. J., Kano, M., Naqvi, H., Paine, P. A., Scott, S. M., Furlong, P. L., Lightman, S. L., Knowles, C. H., & Aziz, Q. (2014). Psychophysiological responses to visceral and somatic pain in functional chest pain identify clinically relevant pain clusters. *Neurogastroenterol Motil*, *26*, 139-148.
- Farmer, A. D., Coen, S. J., Kano, M., Paine, P. A., Shwahdi, M., Jafari, J., Kishor, J., Worthen, S. F., Rossiter, H. E., Kumari, V., Williams, S. C., Brammer, M., Giampietro, V. P., Droney, J., Riley, J., Furlong, P. L., Knowles, C. H., Lightman, S. L., & Aziz, Q. (2013). Psychophysiological responses to pain identify reproducible human clusters. *Pain*, *154*, 2266-2276.
- Ferracuti, S., & De Carolis, A. (2005). Relationships among Eysenck's extraversion, Rorschach's Erlebnistypus, and tolerance of experimental tonic pain (Cold Water Pressor Test). *Percept Mot Skills*, *100*, 237-248.
- IASP. (1994). *Part III: Pain Terms, A Current List with Definitions and Notes on Usage* (Second Edition ed.). Seattle: IASP Press.
- Kehoe, E. G., Toomey, J. M., Balsters, J. H., & Bokde, A. L. (2012). Personality modulates the effects of emotional arousal and valence on brain activation. *Soc Cogn Affect Neurosci*, *7*, 858-870.
- Kumari, V., ffytche, D. H., Williams, S. C., & Gray, J. A. (2004). Personality predicts brain responses to cognitive demands. *J Neurosci*, *24*, 10636-10641.
- Lee, J. E., Watson, D., & Frey Law, L. A. (2010). Lower-order pain-related constructs are more predictive of cold pressor pain ratings than higher-order personality traits. *J Pain*, *11*, 681-691.
- O'Gorman, R. L., Kumari, V., Williams, S. C., Zelaya, F. O., Connor, S. E., Alsop, D. C., & Gray, J. A. (2006). Personality factors correlate with regional cerebral perfusion. *Neuroimage*, *31*, 489-495.
- Ramirez-Maestre, C., & Esteve, R. (2013). Disposition and adjustment to chronic pain. *Curr Pain Headache Rep*, *17*, 312.
- Ramirez-Maestre, C., Lopez Martinez, A. E., & Zarazaga, R. E. (2004). Personality characteristics as differential variables of the pain experience. *J Behav Med*, *27*, 147-165.
- Seifert, F., Schuberth, N., De Col, R., Peltz, E., Nickel, F. T., & Maihofner, C. (2013). Brain activity during sympathetic response in anticipation and experience of pain. *Hum Brain Mapp*, *34*, 1768-1782.

- Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press.
- Tamura, M., Moriguchi, Y., Higuchi, S., Hida, A., Enomoto, M., Umezawa, J., & Mishima, K. (2012). Neural network development in late adolescents during observation of risk-taking action. *PLoS One*, 7, e39527.
- Van Oudenhove, L., Coen, S. J., & Aziz, Q. (2007). Functional brain imaging of gastrointestinal sensation in health and disease. *World J Gastroenterol*, 13, 3438-3445.
- Vassend, O., Roysamb, E., & Nielsen, C. S. (2013). Five-factor personality traits and pain sensitivity: A twin study. *Pain*.
- Walter, S., Kessler, H., Gruss, S., Jerg-Bretzke, L., Scheck, A., Strobel, J., Hoffmann, H., & Traue, H. C. (2011). The influence of neuroticism and psychological symptoms on the assessment of images in three-dimensional emotion space. *Psychosoc Med*, 8, Doc04.
- Yaguez, L., Coen, S., Gregory, L. J., Amaro, E., Jr., Altman, C., Brammer, M. J., Bullmore, E. T., Williams, S. C., & Aziz, Q. (2005). Brain response to visceral aversive conditioning: a functional magnetic resonance imaging study. *Gastroenterology*, 128, 1819-1829.

Table 1: Behavioural Variables for the Low and High Extraversion Groups

Variable	L _E mean ±SEM	H _E mean ±SEM	Difference
Extraversion (0-23)	13 ±0.86	20.05 ±0.32	<i>p</i> <0.0001
Neuroticism (0-24)	8.29 ±1.66	7.68 ±1.47	<i>p</i> =0.79
ST (ml)	8.29 ±2.01	6.63 ±0.79	<i>p</i> =0.40
STAI-S (20-80)	30.93 ±2.10	29.16 ±1.54	<i>p</i> =0.49
STAI-T (20-80)	33.64 ±1.80	34.53 ±2.64	<i>p</i> =0.80
PTT (ml)	21.86 ±2.36	23.16 ±1.40	<i>p</i> =0.62
VAS (0-100)	61.79 ±3.99	66 ±1.81	<i>p</i> =0.30

Table 2

Table 2: Brain Regions Significantly More Active in the High Extraversion Group During Rest, Pain Anticipation and Pain

Size	P Value	X	Y	Z	Side	Brain Region
<i>Rest</i>						
131	0.001	-4	-74	7	Left	Cuneus (BA18)
<i>Anticipation</i>						
183	0.0002	44	-6	13	Right	Insula
<i>Pain</i>						
87	0.0008	50	-22	21	Right	Insula

Table 3

Table 3: Brain Regions Significantly More Active in the Low Extraversion Group During Pain Anticipation

Size	P Value	X	Y	Z	Side	Brain Region
<i>Anticipation</i>						
162	0.0001	20	-72	25	Right	Precuneus (BA31)
96	0.0001	12	-79	-3	Right	Lingual Gyrus (BA18)
86	0.0001	-7	-63	3	Left	Lingual Gyrus (BA18)
84	0.0001	36	-56	-20	Right	Cerebellum (Anterior)
83	0.0002	-29	-70	-26	Left	Cerebellum (Posterior)
69	0.0001	-24	-73	21	Left	Precuneus (BA31)
68	0.0001	40	-63	0	Right	Inferior Temporal Gyrus
50	0.0002	-39	-57	-12	Left	Fusiform Gyrus (BA37)
47	0.0001	-3	-69	47	Left	Precuneus (BA7)
46	0.0001	-22	-67	43	Left	Superior Parietal Lobule (BA7)
44	0.0002	-34	-80	-3	Left	Inferior Occipital Gyrus (BA18)
36	0.0001	15	-64	51	Right	Precuneus (BA7)
34	0.0001	4	-33	63	Right	Paracentral Lobule (BA6)

Table 1: Behavioural Variables for the Low and High Extraversion Groups

With the exception of extraversion scores, no parameters significantly differed between the L_E (n=14) and H_E (n=19) groups.

H_E, high extraversion; L_E, low extraversion; PTT; pain tolerance threshold; ST, sensory threshold; STAI-S, state-trait anxiety inventory-state, STAI-T; state-trait anxiety inventory-trait; VAS, visual analogue scale.

Table 2: Brain Regions Significantly More Active in the High Extraversion Group During Rest, Pain Anticipation and Pain

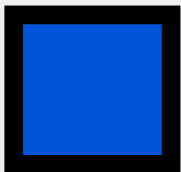
Size of activated clusters represents the number of voxels. Talairach and Tournoux coordinates (x, y, z) are expressed in millimeters. The given coordinates represent the point of maximum activity (highest median response) in each cluster. Clusters are determined by cluster mass statistics, and therefore do not have size limitations.

BA, Brodmann area.

Table 3: Brain Regions Significantly More Active in the Low Extraversion Group During Pain Anticipation

Size of activated clusters represents the number of voxels. Talairach and Tournoux coordinates (x, y, z) are expressed in millimeters. The given coordinates represent the point of maximum activity (highest median response) in each cluster. Clusters are determined by cluster mass statistics, and therefore do not have size limitations.

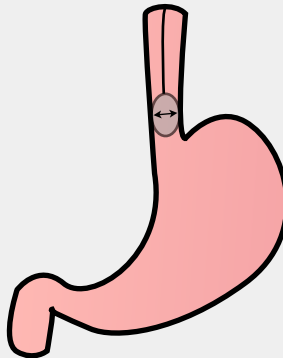
BA, Brodmann area.



Event: *Visual Cue*

Anticipation

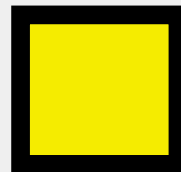
3-12s



Balloon Dilation

Pain

1s



Visual Cue & Pain Rating (VAS)

Safety

VAS

28-35s

Figure 2

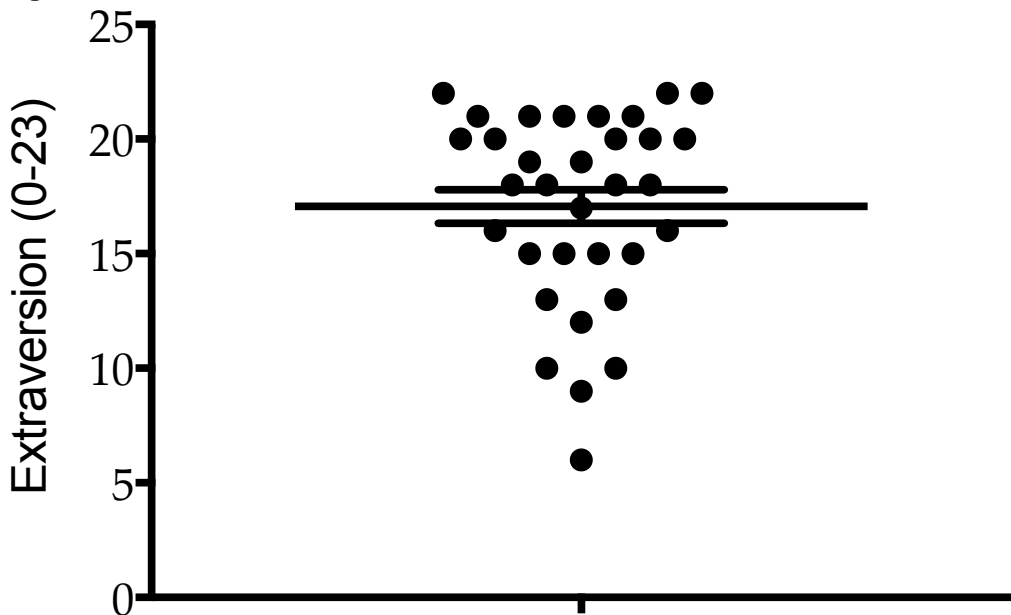
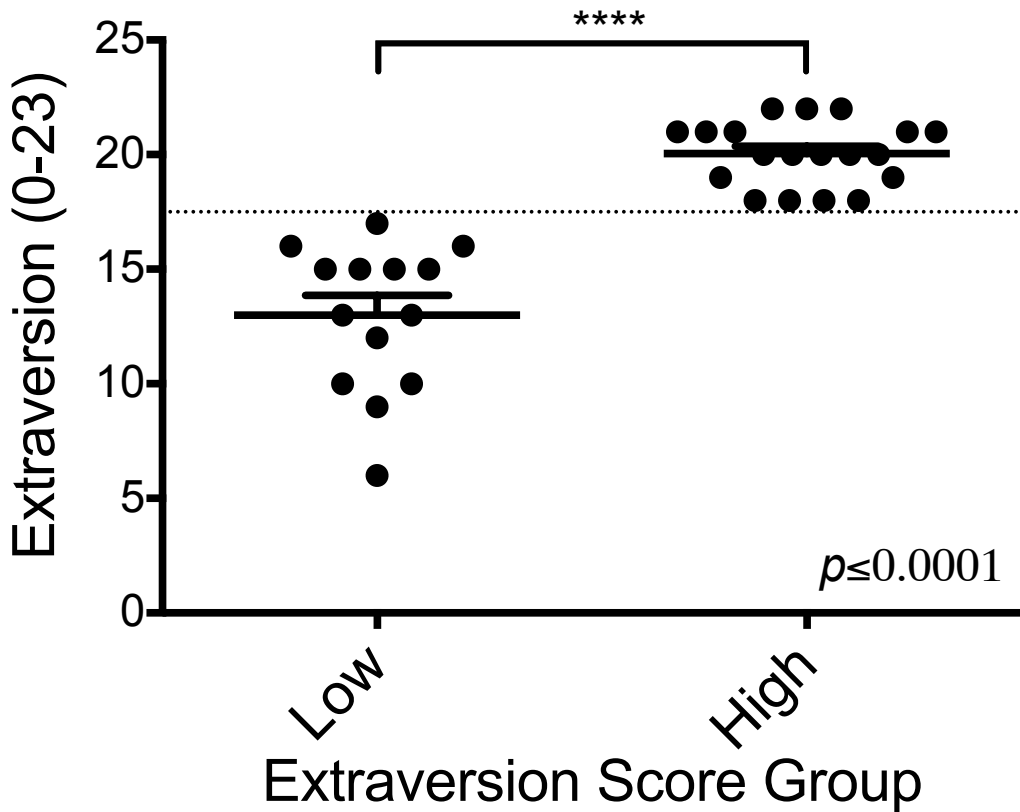
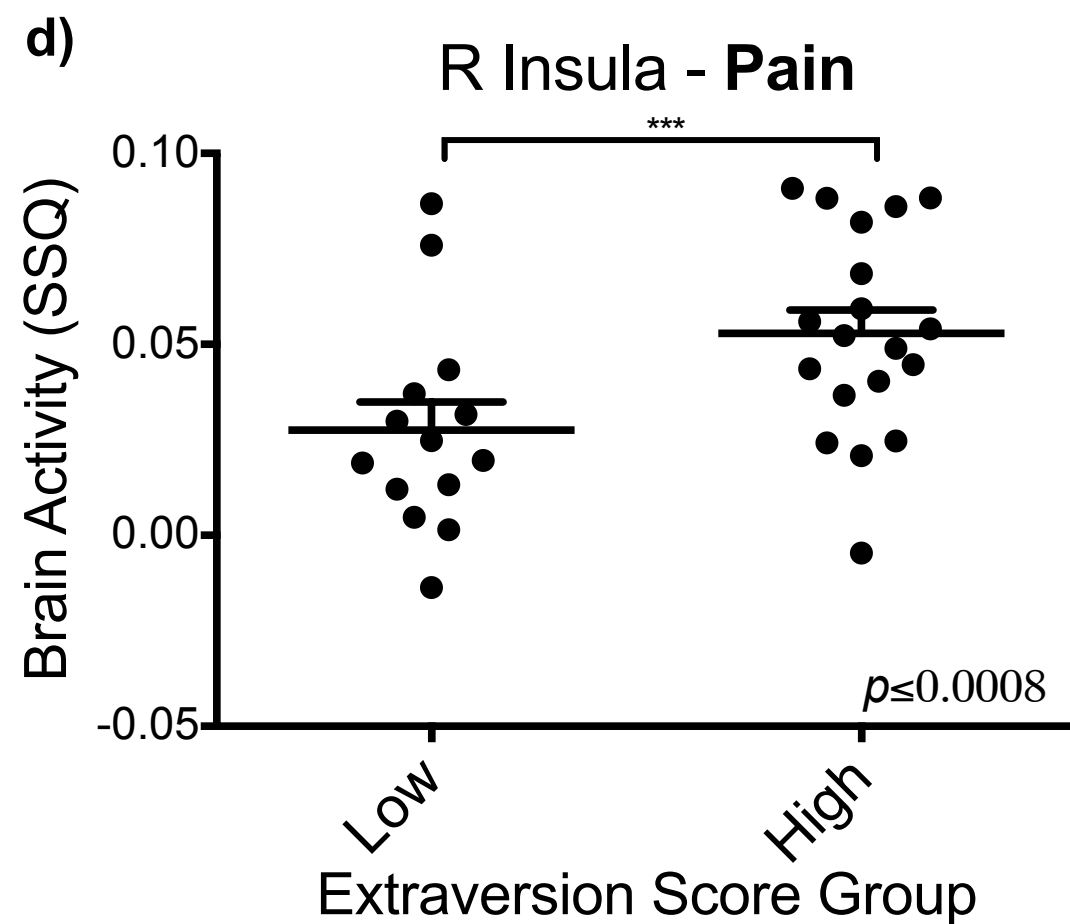
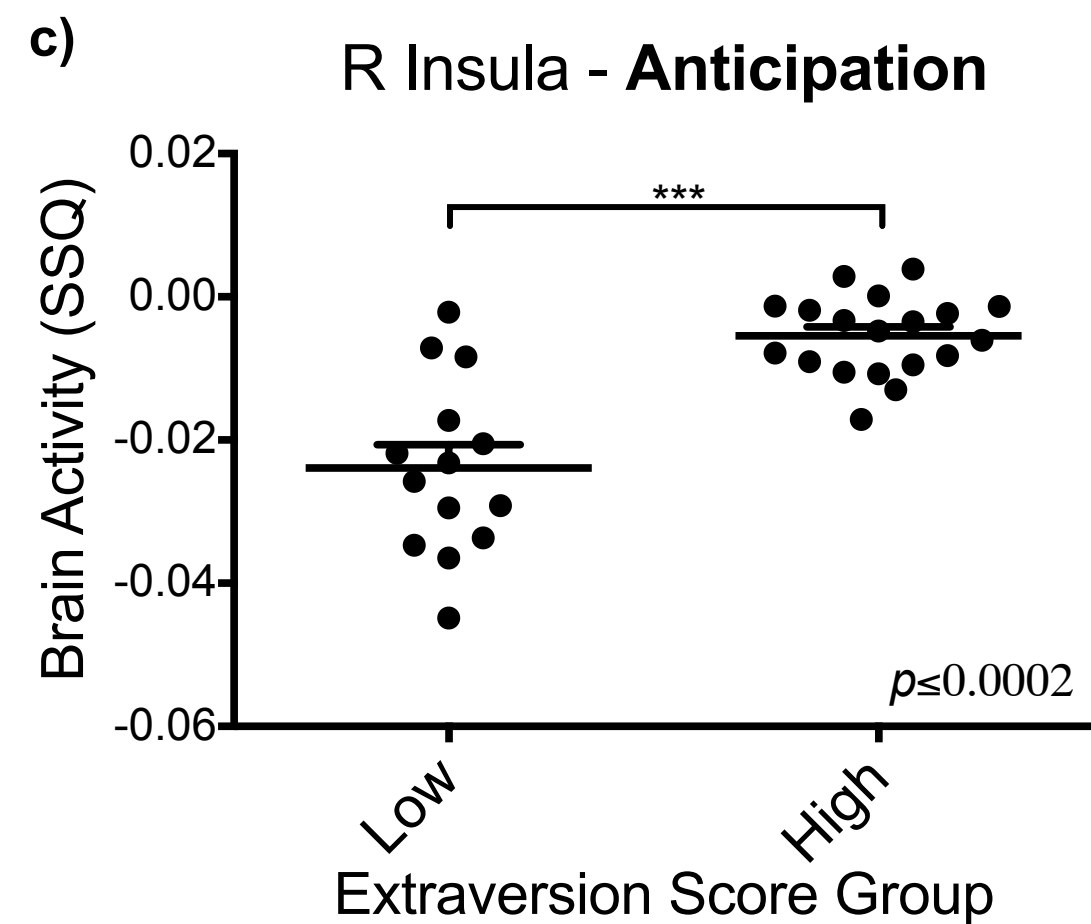
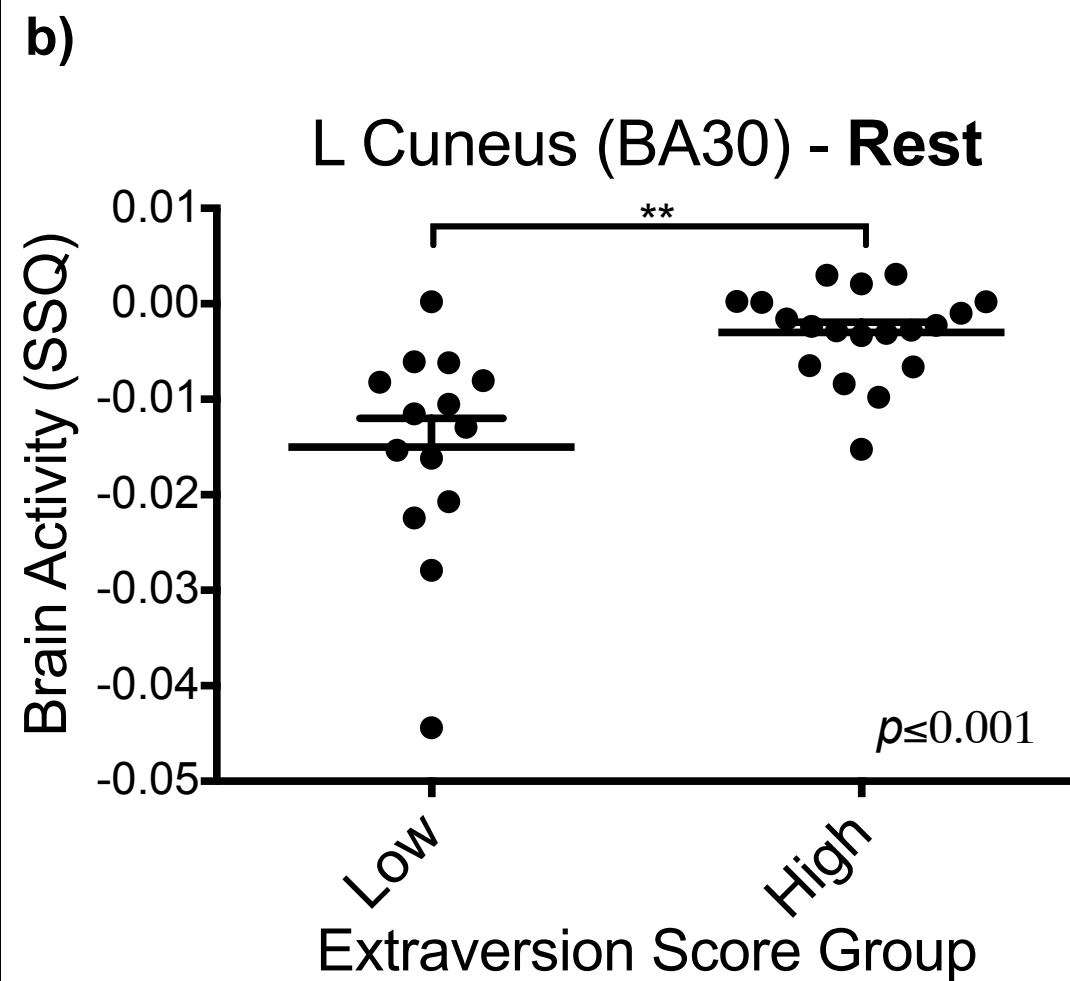
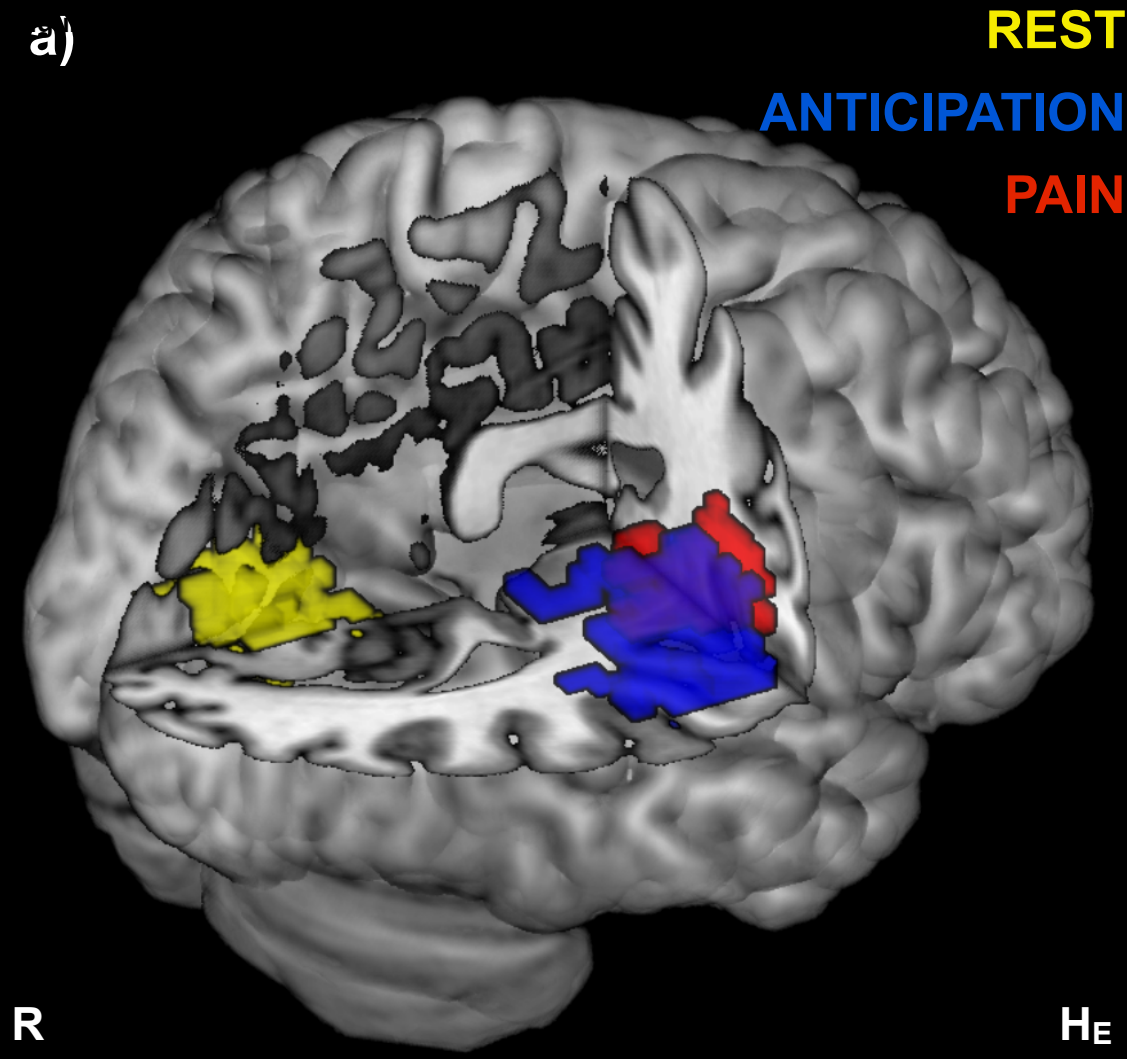


Figure 3





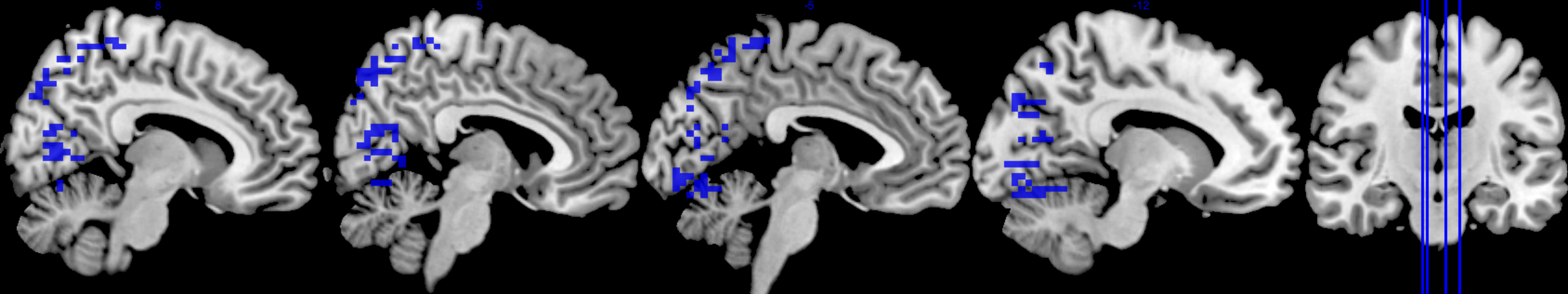


Figure 1: Time Course of a Single Trial

Each trial consisted of 3 events. These were 1) anticipation of pain, 2) visceral pain and 3) safety (from stimulation), where a subject would also give a pain rating (by use of VAS). This event related design was repeated 20 times per subject, whereby the durations of the anticipation and safety events varied throughout to prevent any conditioning which could influence experimental findings. The timings were pseudo-randomised and jittered to the TR (repetition time). In addition, cue colours were randomised to prevent any colour bias.

S, seconds; VAS, visual analogue scale.

Figure 2: Group Extraversion Scores

Graph depicting the mean \pm SEM extraversion scores across the total cohort (n=33).

Figure 3: Low and High Extraversion Group Scores

Graph depicting the significantly different mean \pm SEM extraversion scores in both the L_E (n=14) and H_E (n=19) groups.

Figure 4: Graphical Representation of Brain Regions Significantly More Active in the High Extraversion Group During Rest, Pain Anticipation and Pain

a) 3D render of all regions more active in the H_E group (n=19). Yellow clusters signify greater activity during rest, blue during anticipation, and red during pain. SSQ extractions (the statistical analyses used in the XBAM fMRI analysis package) showing greater activity for the H_E group in the left cuneus during rest (b) and the right insula during both anticipation (c) and pain (d), displaying mean \pm SEM. BA, Brodmann area; H_E, higher extraversion; L, left; R, right; SSQ, sum of squares.

Figure 5: Graphical Representation of Brain Regions Significantly More Active in the Low Extraversion Group During Pain Anticipation

Sagittal multi-slice displaying regions significantly more active in the L_E group (n=14). Blue clusters signify regions of greater activity during anticipation.